## REMARKS

Claims 12, 14, 15, 20, and 21 have been cancelled, without prejudice.

Claim 10 has been amended to recite "[a] process for producing (6R)-2,2,6-trimethyl cyclohexane-1,4-dione (levodione) from ketoisophorone which comprises contacting ketoisophorone with a transformed microorganism expressing NADPH dehydrogenase or a cell-free extract thereof in the presence of NADH or NADPH in an aqueous medium, and isolating the obtained levodione from the reaction mixture, wherein the NADPH dehydrogenase expressed by the transformed microorganism is old yellow enzyme encoded by an oye2 or oye3 gene derived from *Saccharomyces cerevisiae* S288C (ATCC 204508)." Support for this amendment is found in original claim 15 and in the specification at, for example, page 1, lines 1-7 and page 2, lines 12-31. *See In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP §§ 608.01(o) and (l).

It is submitted that no new matter has been introduced by the foregoing amendment. Approval and entry of the amendment respectfully is requested.

## §112, First Paragraph Rejections

### 1. Written Description

Claims 10-14, 16-17, and 20-21 were rejected under 35 U.S.C. §112, first paragraph. (Paper No. 111105 at 2-3). In making the rejection, the Examiner asserted that claims 10-14, 16-17, and 20-21 "contain[ ] subject matter which was not described in specification ...." (*Id.* at 3). The Examiner further asserted that the "claims are directed to methods of producing levodione" using a transformed microorganism

expressing "any" NADPH dehydrogenase or "any" old yellow enzyme. (*Id.*). The Examiner concluded, however, that "the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention." (*Id.*)

With a view towards furthering prosecution, claims 12, 14, 20, and 21 have been cancelled without prejudice and claim 10 has been amended to clarify that "the NADPH dehydrogenase expressed by the transformed microorganism is old yellow enzyme encoded by an oye2 or oye3 gene derived from *Saccharomyces cerevisiae* S288C (ATCC 204508)." It is respectfully submitted that the specification fully supports claim 10 as amended. Indeed, Example 1 discloses the cloning and sequencing of oye2 and oye3. And, Example 2 discloses use of oye2 and oye3 in a transformed microorganism to produce levodione from ketoisophorone in the presence of either NADH or NADPH, (*See, e.g.*, Table 1).

For the reasons set forth above, it is respectfully submitted that the rejection has been rendered moot and should be withdrawn.

**2. Enablement**

Claims 10-14, 16-17, and 20-21 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. (Paper No. 111105 at 3). In making the rejection, the Examiner asserted that the specification "does not reasonably provide enablement for methods of producing levodione from ketoisophorone comprising [a] transformed microorganism expressing *any* NADPH dehydrogenase or *any* old yellow enzyme ...." (emphasis added) (*Id.* at 3-4).

The Examiner acknowledged, however, that the specification is "enabling for methods of producing levodione from ketoisophorone comprising [a] transformed microorganism expressing the *S. cerevisiae* oye encoded by [the] oye2 or oye3 gene ...." (*Id.* at 3) (emphasis added).

With a view towards furthering prosecution, claims 12, 14, 20, and 21 have been cancelled without prejudice and claim 10 has been amended in accordance with the Examiner's determination, namely to recite that "the NADPH dehydrogenase expressed by the transformed microorganism is old yellow enzyme encoded by an oye2 or oye3 gene derived from *Saccharomyces cerevisiae* S288C (ATCC 204508)."

In view of the foregoing, it is respectfully submitted that the rejection has been rendered moot and should be withdrawn.

**Rejections under 35 USC § 102**:

Claims 10-12, 13-14, and 16-17 were rejected under 35 USC § 102(b) as anticipated by Fukuoka *et al.*, EP 1 074 630 A2 ("Fukuoka"). (Paper No. 111105 at 6).

For the reasons set forth below, the rejection, has been rendered moot.

Fukuoka discloses "the microbial production of (6R)-2,2,6-trimethylcyclohexane-1,4-dione [levodione]" by contacting ketoisophorone with one of six specifically enumerated yeast strains:

> (1) *Saccharomyces rouxii* (*Zygosaccharomyces rouxii*) HUT 7191 (IFO 0494);
> (2) *Saccharomyces delbrueckii* HUT 7116 (*Saccharomyces unisporus IFO* 0298);
> (3) *Saccharomyces delbrueckii* (*Torulaspora delbrueckii*) HUT 7102;
> (4) *Saccharomyces willianus* HUT 7106;

(5) *Zygosaccharomyces bailii* ATCC 11486; and
(6) *Candida tropicalis* IFO 1403).

(*See, e.g.*, p. 2, lns. 1-6 and 40-48).

In making the rejection, the Examiner asserted that Fukuoka discloses "the use of immobilized microorganisms (yeast including *Saccharomyces cerevisiae*) to convert ketoisophorone to levodione at pH 4.5- 8.5 and temperature 25-60 °C." (Paper No. 111105 at 6). The Examiner acknowledged that "the yeast disclosed by Fukuoka *et al.* are not disclosed as 'transformed' microorganisms'." (*Id.*). The Examiner contended, however, that "each of these yeast clearly express one or more NADPH dehydrogenases inherently and thus read on the instant claims." (*Id).* The Examiner likewise asserted that "the *S. cerevisiae* disclosed inherently express old yellow enzyme and thus claim 12 is anticipated as well." (*Id.* at 7).

As is well settled, anticipation requires "identity of invention." *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply,* 33 USPQ2d 1496, 1498 (Fed. Cir. 1995). Each and every element recited in a claim must be found in a single prior art reference and arranged as in the claim. *In re Marshall*, 198 USPQ 344, 346 (CCPA 1978); *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.,* 221 USPQ 481, 485 (Fed. Cir 1984). "Moreover, it is incumbent upon the Examiner to ***identify where each and every facet*** of the claimed invention is disclosed in the applied reference." *Ex parte Levy*, 17 USPQ2d 1461, 1462 (BPAI 1990). The Examiner is required to point to the disclosure in the reference "***by page and line***" upon which the claim allegedly reads. *Chiong v. Roland*, 17 USPQ2d 1541, 1543 (BPAI 1990).

Initially, we note that the rejection itself confirms that it cannot be based on §102(b). The Examiner acknowledged that Fukuoka do not disclose using a "transformed microorganism" as recited in amended claim 10. Thus, the Examiner concedes that the method of Fukuoka and the method as recited in claim 10 are not identical. Whether or not the yeast cells disclosed in Fukuoka "inherently" express one or more NADPH dehydrogenases misses the point. Claim 10 is directed to a method, not a composition. Claim 10 recites using a "transformed microorganism" to provide the NADPH dehydrogenase; the Examiner concedes that Fukuoka does not. Accordingly, it is respectfully submitted that the rejection fails to set forth a *prima facie* case under §102 and must be withdrawn for this reason alone.

With a view towards furthering prosecution, however, claims 12 and 14 have been cancelled without prejudice and claim 10 has been amended to recite that "the NADPH dehydrogenase expressed by the transformed microorganism is old yellow enzyme encoded by an oye2 or oye3 gene derived from *Saccharomyces cerevisiae* S288C (ATCC 204508)." The rejection does not and cannot identify where in Fukuoka use of a NADPH dehydrogenase as recited in amended claim 10 is found. Accordingly, it is respectfully submitted that the rejection of claims 10-11, 13, and 16-17 has been rendered moot and should be withdrawn.

Claims 10, 12-13, 16-17, and 20 were rejected under 35 USC § 102(a) as anticipated by Kataoka, M. *et al.*, *"Old Yellow Enzyme from Candida macedoniensis Catalyzes the Stereospecific Reduction of the C=C Bond of Ketoisophorone,"* Biosci. Biotechnol. Biochem, vol. 66, no. 12, pp. 2651-2657 (2002) ("Kataoka"). (Paper No. 111105 at 7).

For the reasons set forth below, the rejection, has been rendered moot.

Kataoka discloses screening a series of microorganisms for "KIP [ketoisophorone]-reducing" activity. (p. 2651-2652). Four strains with "high activities" were selected and their reaction products analyzed on a chiral column and by gas chromatography. (*Id.*, p. 2653). *Candida macedoniensis* AKU4588 was selected "as the source of KIP-reductase forming (6R)-levodione." (*Id.*). Kataoka further discloses that the isolated KIP reductase enzyme from *Candida macedoniensis* AKU4588 may be an "Old Yellow Enzyme (EC 1.6.99.1)" based on "primary structural analysis." (See *id.* p. 2651, 2656, and Fig. 4).

In making the rejection, the Examiner asserted that Kataoka "isolated OYEs (OYE-2 and OYE-3) from *Candida macedoniensis* and stated (page 2653) that *Candida macedoniensis* converts ketoisophorone to levodione at pH 4.5-8.5 and temperature 25-60 °C."[1/] (Paper No. 111105 at 7). The Examiner further asserted that "[w]hile the *Candida macedoniensis* disclosed by Kataoka *et al.* are not disclosed as 'transformed' microorganisms, *Candida macedoniensis* clearly express one or more NADPH dehydrogenases inherently and thus read on the instant claims" and "the *Candida macedoniensis* disclosed inherently express old yellow enzymes (OYE-2 and OYE-3) and thus claims 12-13 are anticipated as well." (*Id.*).

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1/ It is respectfully submitted that the rejection is factually inaccurate to the extent that it characterizes Kataoka as disclosing that it "isolated OYEs (OYE-2 and OYE-3) from *Candida macedoniensis.*" Rather, what Kataoka discloses is that the KIP-reductase from *Candida macedoniensis* that it did isolate was structurally similar to OYE2 and OYE3 from *S. cerevisiae.* Based on this structural similarity (and the similarity to other Old Yellow Enzymes), Kataoka conclude that the KIP-reductase from *Candida macedoniensis* they isolated "belongs to the Old Yellow Enzyme family." (*See*, p. 2655-2656 and Fig. 4). Because the rejection is factually inaccurate, it is respectfully submitted that it should be withdrawn for this reason alone.

As stated above, anticipation requires "identity of invention." *Glaverbel Societe Anonyme,* 33 USPQ2d at 1498. Each and every element recited in a claim must be found in a single prior art reference and arranged as in the claim. *Marshall*, 198 USPQ at 346; *Lindemann Maschinenfabrik,* 221 USPQ at 485.

Initially, we note that Kataoka is not properly cited as prior art against the present claims. The Examiner acknowledged the present application's claim to benefit to International application no. PCT/EP03/01537, which claims benefit to EP application no. 02003968 filed on February 22, 2002. (Paper No. 111105 at 2). Although no date certain (other than "2002") is found in Kataoka, we note that Kataoka was "received" on July 10, 2002 - over five months *after* the priority EP application was filed, and "accepted" on September 5, 2002 - more than seven months *after* the priority EP application was filed. In view of this evidence, it is respectfully submitted that Kataoka is not a proper §102(a) reference. For this reason also the rejection should be withdrawn.

Assuming *arguendo* that Kataoka is a proper §102(a) reference, which it is not, claims 12 and 20 have been cancelled without prejudice and claim 10 has been amended to recite that "the NADPH dehydrogenase expressed by the transformed microorganism is an old yellow enzyme encoded by an oye2 or oye3 gene derived from *Saccharomyces cerevisiae* S288C (ATCC 204508)."

The rejection does not and cannot identify where in Kataoka use of a NADPH dehydrogenase as recited in amended claim 10 is found. For this reason also, it is respectfully submitted that the rejection should be withdrawn.

**Rejections Under 35 USC § 103:**

Claims 10-17 and 20-21 were rejected under 35 USC § 103 as being unpatentable over Vaz, A.D.N. *et al.*, *"Old Yellow Enzyme: Aromatization of Cyclic Enones and the Mechanism of a Novel Dismutation Reaction,"* Biochemistry, vol. 34, pp. 4246-4256 (1995) ("Vaz") in view of Fukuoka and Niino, Y.S. *et al.*, *"A New Old Yellow Enzyme of Saccharomyces Cerevisiae,"* The Journal of Biological Chemistry, vol. 270, no. 5, pp. 1983-1991 (1995) ("Niino"). (Paper No. 111105 at 8).

The rejection respectfully is traversed.

Fukuoka is summarized above.

Vaz discloses various properties relating to the reaction of α,β-unsaturated carbonyl compounds with OYE. (p. 4247). Vaz further disclose transforming *E. coli* with OYE-1, -2, and -3 obtained from "Brewer's Bottom Yeast." (*Id.*). Unless specifically noted, all of the reactions disclosed in Vaz utilized the OYE enzyme obtained from "Brewers Bottom Yeast." (p. 4247). ("Unless otherwise specified, all of the results reported here were obtained with this enzyme.") In Table 1, Vaz disclose the OYE-catalyzed oxidation of NADPH in the presence of various α,β-unsaturated carbonyl compounds, including ketoisophorone (identified in Vaz as "2,6,6-Trimethyl cyclohex-2-ene-1,4-dione"). (*Id.*, p. 4250 and Table 1).

Niino discloses cloning and sequencing OYE3 from *Saccharomyces cerevisiae*. (Abstract; p. 1983; and Figs. 2-4). Niino also disclose expressing the OYE3 in *E. coli*. (*Id.*, p. 1984-1985). Niino further disclose that analysis of purified OYE3 expressed in *E. coli* showed similarities and differences with OYE2. (*Id.*, p. 1983).

In making the rejection, the Examiner asserted that Vaz "teach[es] the use of old yellow enzymes (NADPH dehydrogenase) from yeast (*S. carisbergensis*) or OYEs (including oye2 and oye3) from *S. cerevisiae* for the reduction of [an] olefinic bond (ketoisophorone to levodione)." (Paper No. 111105 at 8).

The Examiner further asserted that Niino "teach[es] genes of OYEs (OYE-2 and OYE-3) from *S. cerevisiae* and transformed *E. coli* expressing these genes" and that Fukuoka "teach[es] the use of immobilized microorganisms (yeast, including *Saccharomyces cerevisiae*) to convert ketoisophorone to levodione at pH 4.5- 8.5 and temperature 25-60 °C." (*Id.*)

The Examiner then summarily concluded that "it would have been obvious ... to use transformed microorganisms taught by Niino *et al.*, which express the OYEs shown by Vaz *et al.* to catalyze the conversion of ketoisophorone to levodione, [and] to convert ketoisophorone to levodione at pH 4.5- 8.5 and temperature 25-60 °C as taught by Fukuoka et al." (*Id.*)

Initially, we note that claims 12, 14, 15, 20, and 21 have been cancelled without prejudice and claim 10 has been amended to recite that "the NADPH dehydrogenase expressed by the transformed microorganism is an old yellow enzyme encoded by an oye2 or oye3 gene derived from *Saccharomyces cerevisiae* S288C (ATCC 204508)."

We further note that it is well settled that the Examiner bears the burden to set forth a *prima facie* case of unpatentability. *In re Glaug*, 62 USPQ2d 1151, 1152 (Fed. Cir. 2002); *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); and *In re*

*Piasecki*, 223 USPQ 785, 788 (Fed. Cir. 1984). If the PTO fails to meet its burden, then the applicant is entitled to a patent. *In re Glaug*, 62 USPQ2d at 1152.

When patentability turns on the question of obviousness, as here, the search for and analysis of the prior art by the PTO must include evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the documents relied on by the Examiner as evidence of obviousness. *McGinley v. Franklin Sports*, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001). The factual inquiry whether to combine documents must be thorough and searching. And, as is well settled, the teaching, motivation, or suggestion to combine "***must be based on objective evidence of record***." *In re Lee*, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002).

The rejection is devoid of *any* evidence - or even argument - in support of the proposed combination. All that is there is a conclusory statement that "it would have been obvious to one of ordinary skill." What the rejection should have done, but did not, was to explain on the record ***why*** one skilled in this art would modify the disclosure of Vaz using Fukuoka and Niino to arrive at the claimed process.

Such an explanation, however, would have run up against the unambiguous teach away in Fukuoka, namely that baker's yeast (the common name for *S. cerevisiae*) is "not suitable for use" (*see*, Fukuoka, p. 2) and Vaz's disclosure that the OYE from Brewer's Bottom Yeast[2/] is sufficient to catalyze oxidation of NADPH in the presence ketoisophorone (see, Vaz, Table 1, p. 4252). Why substitute oye2 or oye3

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[2/] We note that OYE obtained from Brewer's Bottom Yeast is structurally different from either OYE2 or OYE3 obtained from *S. cerevisiae*. *See, e.g.*, Brown *et al.*, *J. Biol. Chem.*, 277(3):2138-2145, 2139 (Figure 1) (2002). We are making Brown of record in the Supplemental Information Disclosure Statement filed concurrently herewith.

obtained from *S. cerevisiae* for the oye obtained from Brewer's Bottom Yeast disclosed in Vaz, especially when Fukuoka discloses that such *S. cerevisiae* is not suitable?

We further note that the rejection fails to consider or identify the factual inquiries required by *John Deere*, including for example, the differences between the prior art and the claimed invention and level of ordinary skill in the art. As the Board has repeatedly held, failure to consider *e.g.*, the differences between the prior art and the claimed invention is grounds for reversal. *Ex parte Tuttle*, 2001 WL 1149812 (unpublished)

> In rejecting claims under 35 U.S.C. § 103, it is incumbent upon the examiner to establish a factual basis to support the legal conclusion of obviousness. *See In re Fine*, 837 F.2d 1071, 1073, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). In so doing, the examiner is expected to make the factual determinations set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), and to provide a reason why one with ordinary skill in the art would have been led to modify or combine prior art references to arrive at the claimed invention. Such reasons must stem from some teaching, suggestion, or implication in the prior art as a whole or knowledge generally possessed by one with ordinary skill in the art. (*Id.* at *2).
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> ***The problem with the examiner's rejection in this case is that the alleged differences between the appellant's claimed invention and Tuttle '375 have not been sufficiently addressed. One of the factual inquiries the examiner must specifically determine under Graham v. John Deere is the differences between the claimed invention and the prior art.*** Here, it is not at all clear what the examiner regards as the differences between the appellant's claimed invention and the disclosure of Tuttle '375. (*Id.* at *3).

Here, as in *Tuttle*, the Examiner failed to identify the differences between the cited documents and the claimed invention. Thus, here as in *Tuttle*, the rejection is legally insufficient to support a rejection under §103. Accordingly, it is respectfully submitted that the rejection should be withdrawn.

Notwithstanding the legally insufficient nature of the rejection, we note that the rejection is also factually insufficient to support a rejection under § 103(a). In doing so we observe that obviousness cannot be based upon speculation, nor can obviousness be based upon possibilities or probabilities. Obviousness ***must*** be based upon facts, "cold hard facts." *In re Freed*, 165 USPQ 570, 571-72 (CCPA 1970). When a conclusion of obviousness is not based upon facts, it cannot stand. *Ex parte Saceman*, 27 USPQ2d 1472, 1474 (BPAI 1993).

Assuming *arguendo* that Vaz is properly combinable with Fukuoka and Niino, which it is not, such a combination does not produce amended claim 10. As noted above, Vaz discloses transforming *E. coli* with oye obtained from Brewer's Bottom Yeast and using the enzyme to catalyze reactions of α,β-unsaturated carbonyls, including ketoisophorone, in the presence of NADPH. The rejection does not - and cannot - identify where in Vaz an OYE encoded by oye2 or oye3 derived from *S. cerevisiae* S288C is used to produce levodione from ketoisophorone in the presence of NADH or NADPH as recited by claim 10. In view of this factual gap, Vaz alone is insufficient to reject the claims under §103.

Unfortunately for the Examiner, neither Fukuoka nor Niino fill this factual gap. As discussed above, Fukuoka discloses the microbial production of levodione by contacting ketoisophorone with one of six specifically enumerated yeast strains - none

of which is the *S. cerevisiae* S288C strain recited in amended claim 10. Niino, on the other hand, is completely silent as to levodione production. Rather, Niino focuses on the initial characterization (*e.g*, cloning and expression) of OYE3. Thus, the proposed combination falls short of filling the factual gap in Vaz. For this reason also the rejection should be withdrawn.

Accordingly, for the reasons set forth above, entry of the amendments, withdrawal of all rejections, and allowance of all claims are respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on May 24, 2006.

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